REMARKS

These remarks are in response to the Final Office Action mailed December 24, 2003. Applicants have amended claims 3, 37, 38 and 43. The amendments are supported throughout the specification as filed. Accordingly, no new matter is believed to have been introduced.

I. REJECTION UNDER 35 U.S.C. §112, FIRST PARAGRAPH

Claims 37-43, 45 and 46 stand rejected under 35 U.S.C. §112, first paragraph, because the specification while being enabling for a method of reducing a cell proliferative disorder associated with glucose starvation in a subject comprising directly delivering a recombinant retroviral vector comprising a nucleic acid construction comprising a functional promoter comprising at least one stress-responsive non-coding regulatory sequence comprising at least two endoplasmic reticulum stress elements (ERSE) as set forth in SEQ ID NO:1 from a rat grp78 coding sequence to a target cell, allegedly does not reasonably provide enablement for treating all cell proliferative disorders in a subject using all routes of administration. The specification allegedly does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected to make and use the invention commensurate in scope with these claims. Applicants respectfully traverse this rejection.

A significant portion of the grounds for the rejection of the claims under 35 U.S.C. §112, first paragraph, is based on the alleged unpredictability of the art of gene therapy in general. The issue of whether the specific instant claims are enabled by the specification should not turn on the state of the art of gene therapy as generally discussed throughout the Office Action. Instead, the relevant question with regard to

enablement of the subject matter of the instant claims is whether the particular steps and materials of the claimed methods are described in the specification in such a way as to enable one skilled in the art to make and use the subject matter as claimed.

The Examiner points to Anderson, Verma, and Vile et al. as an assessment of the state of the art of gene therapy at the time the instant invention was made, citing problems of impracticality and unpredictability that include issues associated with (i) the type of vector and amount of DNA constructs to be administered; (ii) the route and time course of administration, the sites of administration, and successful uptake of the claimed DNA at the target site; (iii) the trafficking of the genetic material within cellular organelles, the rate of degradation of the DNA, the level of mRNA produced, the stability of the mRNA product, the amount and stability of the protein produced, and (iv) what amount of the expressed proteins considered to be therapeutically effective for a DNA therapy method (see, e.g., page 7 of the Office Action; citing to Anderson).

It is respectfully submitted that such a selective reading of Anderson and Verma, in which statements regarding the state of gene therapy in 1997 and 1998 are taken out of context, has resulted in a mischaracterization of the reference that cannot validly be relied on to support an allegation of unpredictability of gene therapy. For example, Anderson also points out that there were 300 clinical trials and approximately 3000 patients that had been treated using gene therapy techniques in 1998. Although Anderson and Verma suggest that gene transfer is not an established clinical treatment regime, it clearly had been demonstrated, based on actual clinical trial data, that therapeutically relevant genes could be transferred

into human patients and be expressed within the patient in such a manner as to show biologic efficacy.

Applicant is not aware of any requirement under current U.S. patent law specifying particular minimum levels of optimization and certified efficacy in order for a treatment-related area of art to qualify as sufficiently "predictable" such that lack of enablement under 35 U.S.C. §112, first paragraph, is not a consideration.

The relevant standard is not that of an established, fully optimized, clinical course of treatment; rather, even in an unpredictable art, a patent application satisfies the requirements of 35 U.S.C. §112, first paragraph, so long as it provides sufficient disclosure, either through illustrative examples or terminology, to teach those of ordinary skill how to make and use the claimed subject matter with reasonable, but not undue, experimentation. There is no requirement that a treatment method achieve a specified level of efficacy or efficiency in order to be considered "enabled" by the specification.

It appears that the Examiner, in asserting the unpredictability of the art of gene therapy, has equated "limitations" in the art in 1997 with "unpredictability." It is respectfully submitted that although methods of gene therapy may be associated with certain limitations and limited success, this does not establish the art as unpredictable. In fact, with respect to methods of gene therapy, the well-studied, -identified and -characterized limitations of the art, as determined through years of research and, several clinical trials, make the methods all the more predictable. The practitioner is well aware of the potential obstacles and clearly knows what he or she is up against in designing and carrying out such therapeutic methods. As such, it is

respectfully submitted, that although the art of gene therapy may not have been a routine, clinical practice at the effective filing date of the subject application, it was not so unpredictable as to qualify as a major factor in the determination of whether the requirements of 35 U.S.C. §112, first paragraph, are satisfied with respect to the instantly claimed subject matter.

Turning now to the rejection of claim 37-43 and 45-46, claims 37 and 38 (upon which claims 39-43, 45 and 46 depend) have been amended to recite in the preamble that the cell proliferative disorder is associated with glucose starvation. Applicants submit that this amendment does not narrow the scope of the claims as presented in the response to the last office action because the last recited element of claims 37 and 38 reflect that the cell proliferative disorder is associated with glucose starvation.

At page 9 the Office Action alleges that the claims are not enabled for "treating"; however, the Examiner indicates that the specification "provides sufficient guidance for . . . using a vector in a method of *reducing* a cell proliferative disorder. . ." Applicants respectfully submit that it appears that the Patent Office is attempting to play the role of the FDA. FDA approval is an important consideration; however, considerations made by the FDA for approving clinical trial are different from those made by the PTO in determining whether a claim is enabled. See, *Scott v. Finney*, 34 F.3d 1058, 1063, 32 USPQ2d 1115, 1120 (Fed. Cir. 1994) ("[t]esting for full safety and effectiveness of a prosthetic device is more properly left to the [FDA]."). In order to advance prosecution, Applicants have amended claim 38 to remove the term "treating" and replace it with "reducing". Accordingly, the claim meets with the Examiner's indication of enablement.

At page 10 the Office Action alleges that the claims read on using "all routes of administration". Claims 38 and 43 have been amended to indicate that the administration is by local and direct administration, respectively.

Applicants believe that the §112, first paragraph rejections in the Final Office Action have been addressed and properly traversed and therefore respectfully request withdrawal of the §112, first paragraph rejections.

II. REJECTION UNDER 35 U.S.C. §112, SECOND PARAGRAPH

Claims 37-43, 45 and 46 stand rejected under 35 U.S.C. §112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular the Office Action indicates that the claims reference "claim 64" and that there is no claim 64 pending in the application. Applicants have amended the claims to remove reference to claim 64. Accordingly, the rejection may be properly withdrawn.

III. REJECTION UNDER 35 U.S.C. §103

Claims 1, 3, 4-9, 15, 16, 31-35, 37-43, 45, 46 and 63 stand rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Gazit et al., (IDS, Cancer Research, 55:1660-1663, 1995) taken with Walther et al., (IDS, Molecular Biotechnology, 6:267-286, 1996) in further view of Mullen (IDS, Pharmac. Ther. 63:199-207, 1994). Applicants respectfully traverse this rejection.

Applicants respectfully submit that the Patent Office has set forth a double standard. On one hand the Patent Office alleges that gene therapy and gene delivery are highly unpredictable arts and thus applicants should not be entitled to

claim genetic delivery methods or gene therapy absent data in specific models under specific conditions. The Patent Office then alleges that it would be a simple matter to arrive at applicants' gene therapy or gene delivery methods and compositions by merely combining the teachings in the art. Such is the case presented here.

The Patent Office indicates at pages 2-3 of the Office Action that Applicants' arguments regarding the provisional disclosure in combination with the skill in the art are not sufficient to enable Applicants' disclosure because of ". . . the relatively incomplete understanding in the biotechnological field involved, e.g., gene therapy. . ." The Office Action than states under the §112 rejection above, that "In view of the art of record at the time the application was filed, gene therapy was considered unpredictable." (See, e.g., page 9, lines 1-2). The Office Action then alleges at page 17,

> However, at the time the invention was made, *cancer pro-drug gene therapy was well known* to one of ordinary skill in the art. . . .
>
> At the time the invention was made it would have been prima facie obvious for a person or ordinary skill to make a vector comprising a nucleic acid encoding an enzyme that converts a non-therapeutically effective compound to a therapeutically effective compound operatively linked to the grp78 promoter . . .
>
> In addition, at the time the invention was made it would have been prima facie obvious for a person of ordinary skill to use the claimed vector in a method of prodrug cancer gene therapy. . .

(Emphasis added). Thus, on the one hand undue experimentation is required to enable gene delivery and gene therapy related to Applicants' invention but at the same time it would have a reasonable expectation of success, because "pro-drug gene therapy was well known".

Applicants respectfully submit that obviousness requires a reasonable expectation of success. *In re Merck & Co., Inc.*, 800 F.2d 1091, 231 USPQ 375 (Fed. Cir. 1986); MPEP §2143.02.

Whether an art is predictable or whether the proposed modification or combination of the prior art has a reasonable expectation of success is determined at the time the invention was made. *Ex parte Erlich*, 3 USPQ2d 1011 (Bd. Pat. App. & Int'f. 1986); MPEP §2143.02. In light of the alleged teachings of the references and the position of the Patent Office, Applicants submit that one of ordinary skill in the art would not have any reasonable expectation of success in combining the alleged vector technology of Gazit with pro-drug gene therapy. Nothing in the art cited by the Examiner indicates success of Applicants' claimed invention or a probability of success, thus it would not have been reasonable to expect the success of the instant invention until it was reduced to practice. Applicants submit that there is no enabling disclosure that provides methods to construct a vector as claimed by Applicants. Furthermore, there is no enabling disclosure that provides evidence that such gene delivery using a vector of the invention can be used to treat tumors. Thus, Applicants have provided a showing there was no reasonable expectation of success thus supporting the position that the claimed invention is nonobviousness. *In re Rinehart*, 531 F.2d 1048, 189 USPQ 143 (CCPA1976); MPEP §2143.02. See also *Amgen, Inc. v. Chugai Pharmaceutical Co.*, 927 F.2d 1200, 18 USPQ2d 1016 (Fed. Cir.), cert. denied, 502 U.S. 856 (1991).

Applicants submit that the combination of references cited by the Examiner is "no more than a plan or invitation for experimentation in view of the art of record exemplifying the unpredictability of gene therapy." (See, the Office Action at the bottom of page 3).

For at least the foregoing reasons, Applicants respectfully request withdrawal of the §103 rejection over the cited references.

Applicant asks that all claims be allowed. Please apply any other charges or credits to Deposit Account No. 06-1050.

Respectfully submitted,

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